REMARKS

Introductory Comments:

Claims 1-3, 5-7, 11, 14-19, 21 and 22 were examined in the Office Action under reply and rejected under 35 U.S.C. §103(a). Claim 22 was objected to based on a typographical error. The rejections are respectfully traversed for reasons discussed below.

Applicants note with appreciation the withdrawal of the previous rejection under 35 U.S.C. §103(a) over U.S. Patent No. 5,900,238 to Gombotz et al., in view of Partidos et al., *Immunology* (1996) 89:483-487 ("Partidos") and EP 517,565 to Callegaro et al. ("Callegaro").

Overview of the Above Amendments:

Claim 22 has been amended to correct a typographical error. Amendment of this claim is made without intent to abandon any originally claimed subject matter and without intent to acquiesce in any rejection of record.

Rejection Under 35 U.S.C. §103(a):

All claims stand rejected under 35 U.S.C. §103(a) as obvious over Callegaro in view of both Partidos and Koichiro, JPO 015163161, abstract ("Koichiro"). The Office asserts Callegaro teaches "that hyaluronic acid is a known and widely used polymeric carrier for release systems for pharmacologically active molecules." Office Action, page 4. The Examiner correctly acknowledges that Callegaro fails to teach "the claimed antigen or the inclusion of LT-K63." Office Action, page 4. Partidos is said to teach LT-K63 as an effective mucosal adjuvant. Koichiro is said to teach "an influenza vaccine comprising hyaluronic acid." Office Action, page 5. The Examiner notes that Koichiro fails to teach the particular structure of the hyaluronic acid, but asserts that Koichiro demonstrates "that influenza antigen is compatible with hyaluronic acid compositions." Office Action, page 5. However, applicants submit that the Office has failed to present a *prima facie* case of obviousness.

As previously explained, three basic criteria must be met in order to establish a *prima facie* case of obviousness. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference(s). Second, there must be a reasonable expectation of success. Finally, the prior art reference(s) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Applicants submit that the cited combination fails to satisfy these criteria. Thus, a *prima facie* case of obviousness has not been presented by the Office.

The Office extends the teachings of the primary reference, Callegaro, in too simplistic a manner. Not only does Callegaro fail to teach the use of an influenza antigen, the reference nowhere even mentions that hyaluronic acid microspheres could be used to deliver vaccine antigens. The examples in Callegaro pertain only to therapeutic proteins which act in a wholly different manner. The complicated mechanisms involved in an immune response such as mucosal immunity, and the particular problems encountered and hurdles to be overcome for successful vaccine delivery, are nowhere addressed in Callegaro. There is simply no recognition in Callegaro that vaccine antigens could be delivered using hyaluronic acid compositions.

The secondary references fail to provide the missing link. Partidos pertains to intranasal administration of a measles virus epitope in combination with LTK63. Neither the epitope or LTK63 is in any way associated with a delivery particle such as a hyaluronic acid microsphere as claimed herein and there is not even a hint in the reference to do so. The Koichiro abstract states the influenza vaccine contains hyaluronic acid or its salt. However, as the Office notes, the reference is silent regarding the form of the hyaluronic acid present. Thus, the use of a hyaluronic acid ester polymer or a crosslinked derivative of hyaluronic acid, as claimed in the instant application, is not suggested. Moreover, there is no discussion regarding whether the antigen is adsorbed, entrapped or present in the free state.

Applicants, on the other hand, have found that the unique combination of an antigen adsorbed to a microparticle formed from a hyaluronic acid ester or a crosslinked derivative of hyaluronic acid, in combination with an adjuvant, provides a significantly greater immune response than the use of the antigen or the antigen and adjuvant alone (see the examples in the present application). The cited art combination nowhere suggests that this is the case. Although the cited references disclose bits and pieces of the claimed invention, the glue that holds those pieces together is missing. Even if individual elements of the invention are taught in the prior art, such is not, in and of itself, sufficient to make out a case of *prima facie* obviousness. See, *Symbol Technologies, Inc. v. Opticon, Inc.*, 19 USPQ2d 1241 (Fed. Cir. 1991) ("We do not pick and chose among the individual elements of assorted prior art references to recreate the claimed invention, but rather, we look for some teaching or suggestion in the references to support their use in the particular claimed combination."). As stated by the Court of Appeals for the Federal Circuit, "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). See, also, *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988): "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."

Based on the discussion above, applicants submit that the cited combination is indeed based on impermissible hindsight reconstruction and that there is no suggestion or motivation in the prior art to combine the references. Thus, a *prima facie* case of obviousness has not been presented by the Office. The Office is respectfully requested to withdraw this rejection.

CONCLUSION

Applicants respectfully submit that the claims are novel and nonobvious over the art and comply with the requirements of 35 U.S.C. §101 and §112. Accordingly, allowance is believed to be in order and an early notification to that effect would be appreciated.

Please direct all further communications in this application to:

Alisa A. Harbin, Esq.
Chiron Corporation
Intellectual Property – R440
P.O. Box 8097
Emeryville, CA 94662-8097
Telephone: (510) 923-2708
Facsimile: (510) 655-3542

Respectfully submitted,

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By: _____

Roberta L. Robins
Reg. No. 33,208
Attorney for Applicants

Chiron Corporation
Intellectual Property – R440
P.O. Box 8097
Emeryville, CA 94662-8097

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claim 22 has been amended as follows:

22. (Amended) The composition of claim 11, wherein the [microshphere] microsphere is a nanosphere.

CURRENTLY PENDING CLAIMS

1. (Twice Amended) A composition comprising an hyaluronic acid ester polymer in the form of a microsphere, a detoxified mutant of a bacterial ADP-ribosylating toxin, and a selected antigen, wherein said antigen is present in an amount of approximately .1% to about 40% (w/w) antigen to hyaluronic acid polymer, and wherein the antigen is not entrapped in the microsphere.

2. The composition of claim 1, wherein said antigen is present in an amount of approximately 2% to about 25% (w/w) antigen to hyaluronic acid polymer.

3. The composition of claim 1, wherein the hyaluronic acid ester is selected from the group consisting of an hyaluronic acid where from about 75% to about 100% of free carboxyl groups are esterified with one or more alkyl groups, and a crosslinked derivative of hyaluronic acid in which about 0.5% to about 20% of the carboxyl groups of the hyaluronic acid polymer are crosslinked to hydroxyl groups of the same or a different hyaluronic acid molecule.

5. The composition of claim 1, wherein the detoxified mutant of a bacterial ADP-ribosylating toxin selected from the group consisting of LT-K63 and LT-R72.

6. The composition of claim 1, wherein the selected antigen is a viral antigen.

7. The composition of claim 6, wherein the selected antigen is an influenza antigen.

11. (Amended) A composition comprising (a) a microsphere comprised of an hyaluronic acid ester polymer selected from the group consisting of an hyaluronic acid where from about 75% to about 100% of free carboxyl groups are esterified with one or more alkyl groups, and a crosslinked derivative of hyaluronic acid in which about 0.5%

to about 20% of the carboxyl groups of the hyaluronic acid polymer are crosslinked to hydroxyl groups of the same or a different hyaluronic acid molecule; (b) a selected antigen adsorbed to the microsphere, wherein said antigen is present in an amount of approximately 2% to about 25% (w/w) antigen to hyaluronic acid polymer; and (c) an immunological adjuvant.

14. A method of making a pharmaceutical composition which comprises combining the composition of claim 1 with a pharmaceutically acceptable mucosal excipient.

15. A method of making a pharmaceutical composition which comprises combining the composition of claim 11 with a pharmaceutically acceptable mucosal excipient.

16. A method of immunization which comprises mucosally administering a therapeutically effective amount of the pharmaceutical composition of claim 14 to a vertebrate subject.

17. A method of immunization which comprises mucosally administering a therapeutically effective amount of the pharmaceutical composition of claim 15 to a vertebrate subject.

18. The method of claim 16 wherein the administering is done intranasally.

19. The method of claim 17 wherein the administering is done intranasally.

21. The composition of claim 1, wherein the microsphere is a nanosphere.

22. (Amended) The composition of claim 11, wherein the microsphere is a nanosphere.